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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,344	12/04/2001	Loren J. Miraglia	ISPH-0622	8099

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/005,344	MIRAGLIA ET AL.
	Examiner	Art Unit
	Terra C. Gibbs	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,10,11 and 51-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10,11 and 51-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

This Office Action is a response to Applicant's Remarks and Amendment filed August 8, 2003.

Claims 9 and 12-50 have been canceled. New claims 51-59 are acknowledged.

Claims 1-3, 5-8, 10, 11, and 51-59 are pending in the instant application.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 5 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn in view of Applicants amendment to correct for improper antecedent basis.**

Claim Rejections - 35 USC § 102

Claims 1-3 were rejected under 35 U.S.C. 102(b) as being anticipated by Kondo et al. (Oncogene, 1995 Vol. 10:2001-2006). **This rejection is withdrawn in view of Applicants amendment to the claims to delete "coding region", filed August 8, 2003.**

Claims 1-3 were rejected under 35 U.S.C. 102(b) as being anticipated by Kondo et al. (British Journal of Cancer, 1996 Vol. 74:1263-1268). **This rejection is withdrawn**

in view of Applicants amendment to the claims to delete "coding region", filed August 8, 2003.

Claims 1-3 were rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al. (Proceedings of the National Academy of Science, 1998 Vol. 95:195-200). **This rejection is withdrawn in view of Applicants amendment to the claims to delete "coding region", filed August 8, 2003.**

Claims 1-3 were rejected under 35 U.S.C. 102(b) as being anticipated by Teoh et al. (Blood, 1997 vol. 5:1982-1992). **This rejection is withdrawn in view of Applicants amendment to the claims to delete "coding region", filed August 8, 2003.**

Claim 1 is rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Landers et al. (Cancer Research, 1997 Vol. 57:3562-3568). **This is a new rejection.**

Landers et al. disclose a mdm2 primer of the following sequence: 5'-CAGGTCAACTAGGGGAAATAAG-3' (see page 3563, first column). This primer is reverse complementary to bases 1796-1775 of SEQ ID NO:1 of the instant invention. Since the primer of Landers et al. meets all the structural requirements of the instant claims, the primer would also be expected to specifically hybridize to nucleic acid encoding human mdm2, as per applicant's definition set forth in the specification as filed, page 13, lines 20-33 and page 14, lines 1-3.

Furthermore, since the prior art primer meets all the structural limitations of the claims, the prior art primer would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."

Therefore, the instant invention is anticipated or obvious over Landers et al.

Claim Rejections - 35 USC § 103

Claims 1-3, 6-8, 10 and 11 were rejected under 35 U.S.C. 103(a) as being unpatentable over Burrell et al. (WO 93/20238) in view of Branch (TIBS, February 1998 Vol. 23, pages 45-50) and Monia et al [U.S. Patent No. 5,872,242]. **This rejection is maintained for the reasons of record set forth in the previous Office Action, filed January 9, 2003.**

Applicants argue that there is no motivation to combine the cited references, and, even if combined, the claimed invention would not be produced. Applicants argue that in

established a prima facie case of obviousness, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to combine reference teachings to arrive at the claimed invention. Applicants argue that the motivation must stem from some teaching, suggestion or inference in the prior art and not from appellants' disclosures. Applicants argue that the Office Action identifies no motivating force that would impel one of skill in the art to combine teachings to achieve the claimed invention. Applicants argue that there is no motivation to lead one skilled in the art to combine the teachings of Branch and Burrell. Applicants contend that the previous Office Action selectively relies on Burrell et al. for teaching the human mdm2 transcript sequence, on Branch for designing small antisense oligonucleotides, and on Monia et al. for teaching oligonucleotide modifications. Applicants argue that this selective reliance is improper and based on hindsight reasoning.

Applicant's arguments have been fully considered, but are not found persuasive. The Examiner agrees with the Applicants in contending that Burrell et al. was relied upon for teaching the human mdm2 sequence, Branch was relied upon for teaching the design of small antisense oligonucleotides and Monia et al. was relied upon for teaching oligonucleotide design and modification. Burrell et al. teach the entire antisense transcript of human mdm2. Branch teach the favored size of an antisense oligonucleotide to maximize target specificity, as smaller antisense oligonucleotides bind to non-specific targets. Monia et al. teach oligonucleotide design, synthesis, and modification.

The Examiner believes that Burrell et al. provides a clear motivation force that would impel one of skill in the art to combine teachings to achieve the claimed invention. For example, see the previous Office Action at page 9 (mid-page) "This reference

[Burrell et al.] goes on to teach that identifying means to inhibit the expression of mdm2 would have great therapeutic benefits". The previous Office Action (at page 9, mid-page) also discloses, "antisense oligonucleotides targeted to unprocessed pre-mRNA or processed mRNA encoding mdm2 can be used to inhibit translation of mdm2".

As stated in the previous Office Action, it would have been obvious to one of ordinary skill in the art to modify the teachings of Burell et al. to design antisense oligonucleotides of at least 17 nucleobases in length (Branch), modifying those antisense oligonucleotides with phosphorothioate linkages, 2'-methoxyethoxy modified sugar residues, and a 5'-methylcytosine modified nucleobase (Monia et al.), in order to maximize target site specificity (Branch), and increase hybridization efficiency as well as maintaining nuclease resistance of said antisense oligonucleotide (Monia et al.). Additionally, it would have been obvious to design antisense oligonucleotides targeting the 5' untranslated region, translation termination codon region or 3' untranslated region of an mRNA in order to interfere with all the vital functions of an mRNA according to Monia et al. Moreover, one of ordinary skill in the art would have been motivated to design antisense oligonucleotides of at least 17 nucleobases comprising the modifications taught by Monia et al. since oligonucleotides of this size possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides.

It is noted that there is no evidence of record to show any such differences between the human mdm2 sequence of Burrell et al. and SEQ ID NO:1 of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to a 5'-untranslated region, intron:exon junction,

intron region, translation termination codon region or 3'-untranslated region of human mdm2 (SEQ ID NO:1) of the instant invention, since designing antisense oligonucleotides was well known in the art at the time of filing.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing over Burell et al. in view of Branch, and Monia et al.

Claims 1-3, 6-8, 10 and 11 were rejected under 35 U.S.C. 103(a) as being unpatentable over either Chen et al. (Proceedings of the National Academy of Science, 1998 Vol. 95:195-200), Teoh et al. (Blood, 1997 vol. 5:1982-1992), Kondo et al. (Oncogene, 1995 Vol. 10:2001-2006), Kondo et al. (British Journal of Cancer, 1996 Vol. 74:1263-1268) in further view of Monia et al. [U.S. Patent No. 5,872,242]. **This rejection is withdrawn in view of Applicants amendment to the claims to delete "coding region", filed August 8, 2003.**

Claims 5 and 51-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burrell et al. (WO 93/20238) in view of Bennett et al [U.S. Patent No. 6,172,216]. **This is a new rejection.**

Claims 5, 51 and 52 are drawn to an antisense compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region or 3'-untranslated region of a nucleic acid molecule encoding human mdm2 (SEQ ID NO:1), wherein the antisense compound modulates the expression of mdm2, wherein at least on 2'-O-methoxyethyl modification is in a cytidine;

and in which every 2'-O-methoxyethyl modified cytidine is a 5-methyl cytidine. Claim 53 and 54 are drawn to an antisense compound 8 to 30 nucleobases in length targeted to the coding region or exon region of a nucleic acid molecule encoding mdm2, wherein the compound is a chimeric phosphorothioate oligonucleotide comprising 2'methoxyethyl wings and a deoxy gap, and inhibits mdm2 expression by at least 60%. Claims 55-59 are dependent on claim 53 and include all the limitations of claim 53, with the further limitations wherein the antisense compound comprises at least one 5-methyl cytidine, wherein at least one 2-'methoxyethyl modification is in a cytidine, and in which every 2'-O-methoxyethyl modified cytidine is a 5-methyl cytidine.

Burrell et al. teach the entire antisense transcript of mdm2 and further teach that antisense oligonucleotides targeted to unprocessed pre-mRNA or processed mRNA encoding mdm2 can be used to inhibit translation of mdm2 (p. 10). Burrell et al. also teach that the mdm2 gene functions in tumorigenesis, and that over expression of mdm2 causes cells to escape from p-53 regulated growth (p. 4). This reference goes on to teach that identifying means to inhibit the expression of mdm2 would have great therapeutic benefits (p. 10). However, Burrell et al. does not teach antisense oligonucleotides targeting the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region or 3'-untranslated region of a nucleic acid molecule encoding human mdm2 (SEQ ID NO:1), wherein said antisense oligonucleotide comprises 8 to 30 nucleobases or comprising the modifications of antisense oligonucleotides according to the present invention. Burrell et al. also do not teach an antisense compound 8 to 30 nucleobases in length targeted to the coding region or exon region of a nucleic acid molecule encoding mdm2, wherein the compound is a chimeric phosphorothioate

oligonucleotide comprising 2'methoxyethyl wings and a deoxy gap, and inhibits mdm2 expression by at least 60%.

Bennett et al. teach antisense oligonucleotides that can specifically hybridize with different regions in a target gene, including a 5'-untranslated region, intron:exon junction, intron region, translation termination codon region or 3'-untranslated region (see column 3, lines 57-67 and column 4, lines 1-62 and Tables 1 and 2). Bennett et al. further teach a wide range of antisense oligonucleotides that inhibit gene expression at various inhibition capacities, including inhibition by at least 60% (see Tables 1 and 2). Bennett et al. further teach antisense oligonucleotides with modified nucleobases, such as 2'-O-methoxyethyl modified amidites, wherein at least one 2'-O-methoxyethyl modification is in a cytidine; and in which every 2'-O-methoxyethyl modified cytidine is a 5-methyl cytidine (see column 16, lines 64-67, and column 18, lines 30-44). Bennett et al. finally teach antisense oligonucleotides as chimeric oligonucleotides comprising 2'methoxyethyl wings and a deoxy gap (see column 28, lines 51-59 and Tables 3 and 4). Bennett et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have made and used an antisense compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region or 3'-untranslated region of a nucleic acid molecule encoding human mdm2 (SEQ ID NO:1), wherein the antisense compound modulates the expression of mdm2, wherein at least on 2'-O-methoxyethyl modification

is in a cytidine; and in which every 2'-O-methoxyethyl modified cytidine is a 5-methyl cytidine. One of ordinary skill in the art would have been motivated to make antisense oligonucleotides targeted to a 5'-untranslated region, intron:exon junction, intron region, translation termination codon region or 3'-untranslated region of a nucleic acid molecule targeted to human mdm2 using the sequence taught by Burrell et al. and the motivation of Bennett et al. to target different regions in a target gene. One of ordinary skill in the art would have expected success in making antisense compound 8 to 30 nucleobases in length targeted to the coding region or exon region of a nucleic acid molecule encoding mdm2, wherein the compound is a chimeric phosphorothioate oligonucleotide comprising 2'methoxyethyl wings and a deoxy gap, and inhibits mdm2 expression by at least 60% since Bennett et al. demonstrate that following generic teachings of making antisense oligonucleotides to a target, it would be expected that oligonucleotides will inhibit by at least 60% since a wide range of oligonucleotides of various capacities are created and inhibit gene expression to various degrees, including by at least 60% (see Bennett et al. Tables 1 and 2). One of ordinary skill in the art would have been motivated to modify the antisense oligonucleotides because Bennett et al. taught antisense oligonucleotides with modified bases confer increased nuclease resistance, increased uptake in cells and increased binding affinity for an mRNA target.

It is noted that there is no evidence of record to show any such differences between the human mdm2 sequence of Burrell et al. and SEQ ID NO:1 of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to a 5'-untranslated region, intron:exon junction, intron region, translation termination codon region or 3'-untranslated region of human

mdm2 (SEQ ID NO:1) of the instant invention, since designing antisense oligonucleotides was well known in the art at the time of filing.

Double Patenting

Claims 1-3, 6-8, 10 and 11 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,238,921 ('921) and claims 1-20 of U.S. Patent No. 6,184,212 ('212). **This rejection is maintained for the reasons of record set forth in the previous Office Action, filed January 9, 2003.**

Applicants argue that the previous Office Action mistakenly concluded that because a species anticipates a genus, the subject matter of claims 1-3, 6-8, 10 and 11 is obvious in view of ('921) and ('212). Applicants further argue that both the ('921) and the ('212) patents have the same priority date as the present application and thus, neither ('921) nor ('212) are prior art for purposes of an anticipation rejection or obviousness rejection.

The Examiner agrees with Applicant in stating that the previous Office Action mistakenly concluded that a species anticipates a genus. MPEP § 2131.02 was used out of context in the previous Office Action. However, the claims remain rejected because although the conflicting claims are not identical, they are not patentably distinct from each other because an antisense compound 8 to 30 nucleobases in length targeted to nucleobases 1-308 of the 5'-untranslated region, 1776-1806 of the translation termination codon region or 1818-2370 of the 3'-untranslated region of a nucleic acid encoding human mdm2, of ('212') encompasses the antisense compound 8 to 30 nucleobases in

length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region or 3'-untranslated region of a nucleic acid molecule encoding human mdm2 of the instant invention. Similarly, the oligonucleotide up to 50 nucleotides in length comprising SEQ ID NOs: 3, 4, 5, 7, 15, 17, 18, 19, or 21 that inhibits the expression of human mdm2 of ('921) encompasses the antisense compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region or 3'-untranslated region of a nucleic acid molecule encoding human mdm2 of the instant invention. Therefore, the application and the patents claim the same inventive concept.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
October 28, 2003

Karen A. Lacourciere
KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER